The NICHD and the Best Pharmaceuticals for Children Act (BPCA)

Presented by Donald Mattison to the National Advisory Child Health and Human Development (NACHHD) Council

January 2004

National Institutes of Health (NIH)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Contemporary Drug Development

- Opportunity for profit
- Frequency, severity, chronicity of disease
- Pathophysiology of disease
  - Target sites for intervention
  - Molecular design for target
  - Roles of target outside of disease being treated
- Pre-clinical testing for efficacy, safety, pk/pd
  - Developmental toxicity testing?;
    - 3 Segment testing
    - Developmental role of target(s) of the molecular entity
- Clinical testing for efficacy and pk/pd
  - Developmental Toxicity & Safety?
- FDA Approval
- Aggressive marketing and distribution

Pediatric *"Drug Development"*

- Drugs initially designed & tested for adult diseases
  - Pre-clinical & clinical testing in adults for;
    - Efficacy (pharmacokinetics, pharmacodynamics)
    - Safety (with focus on mature animals & humans!)
- Used *off-label* in pediatric populations (age, indication)
  - ? PK, ?? Dosing, ??? Efficacy, ???? Safety
  - Developmental changes in ADME?
  - Function & expression of target receptor(s) in children?
  - Pathophysiology of disease in children?
  - Long-term consequences for growth & development

FDA/NIH Partnership

- **Best Pharmaceuticals for Children Act (BPCA) was signed January 4, 2002**
  - BPCA establishes a process for studying "*on-patent*" as well as "*off-patent*" drugs
  - FDA/NIH collaboration on scientific, clinical, study design, weight of evidence, ethical, & labeling issues -- ***to improve pediatric therapeutics***

BPCA: On-patent Drugs

- Renews exclusivity if requested studies conducted by manufacturer
- Referral the Foundation for NIH if sponsor declines requested studies
  - Funding for studies *"may"* come, completely or in part from Foundation for NIH
  - Industry *"promised"* to provide funding for on-patient drug studies declined by industry
  - Funding from industry (or even private individuals) to be donated to Foundation for NIH (501c3)
  - Current amount at FNIH ~$ 3 million

BPCA: Off-patent Drugs

- NIH develops on regular basis (at least annually), an updated list of off-patent therapies which *"most urgently"* require study in pediatric populations for label modifications
- Establishes procedure to study off-patent drugs from priority list in collaboration with FDA and Institutes
  - Funding for BPCA at NIH is distributed among many institutes (~25% to NICHD)
  - NICHD organizes study design team with FDA & relevant institutes
  - NICHD has primary responsibility; organization, contracting, monitoring, IND, data for potential label modification, draft label modification for specific ages and indications

Institutes Supported by BPCA!

- NCI
- NHLBI
- NIDCR
- NIDDK
- NINDS
- NIAID
- NICHD
- NEI
- NIEHS
- NIAMS
- NIDCD
- NIMH
- NIDA
- NIAAA
- NINR
- NHGRI
- NCRR
- NCAM
- FIC

Prioritized Listing: Historical

- In developing lists NIH consulted;
  - FDA Divisions and Advisory committees
  - NIH Institutes and Centers conducting pediatric research
  - Experts in pediatrics, pharmacoepidemiology, pharmacology, toxicology, etc…
- Preliminary list of off-patent drugs drafted and categorized by indication and use
- Drugs prioritized based on;
  - Frequency of use in pediatric population
  - Potential for pediatric public health benefit

Improving the Listing Process

- Frequency of conditions & diagnosis
  - Mortality, morbidity, life-course impact
  - Pathophysiology
  - In-patient and out-patient mix
  - Disparities, age, temporal & regional differences
  - Anticipating future therapeutic needs
- Frequency of medication use
  - Disparity of use
  - Temporal, regional differences
  - Age of child
  - Medications not currently used in pediatric diseases
- Professional & public participation
- Critical Label evaluation; indications & ages

Options for Peds Drug Development

- Formulations
- Development of clinical tools, clinical trials
  - Ethical issues
  - Infrastructure
- Add-on studies to current NIH studies
- Conduct studies within existing NIH networks
- Strategic thinking about future studies
  - Rapid, economical & efficient trial design, pre-clinical testing, existing molecular entities needing evaluation, data on frequency of conditions and therapy use, consequences of long term use

Current BPCA Success!

- Listing Activities
- Written Requests prepared
- Requests for Contracts – Requests for Proposals
- Proposals reviewed and awarded
- Special activities being conducted under BPCA

Current BPCA Success!

- Listing Activities
  - Two lists have been published
  - Third listing has been finalized
  - New listing process being developed
    - Dr Tamar Lasky

Current BPCA Success!

- **Written Requests**
  - Written requests are the mechanism by which FDA notifies drug manufacturers of additional data needs
  - Written requests for off-patent drugs are developed collaboratively with FDA, and the relevant participating institute
  - Written requests for on-patent drugs are developed by FDA and if declined by industry are then referred to FNIH

Current BPCA Success!

- Written Requests
  - Off-Patent Written Requests referred to NIH
    - 8 drug/indication pairs
  - On-Patent Written Requests referred to FNIH
    - Morphine – pain
    - Buproprion – depression and smoking cessation
    - Sevelamer – hyperphosphatemia and chronic renal insufficiency
    - Zonisamide – partial seizures

Current BPCA Success!

- Off-Patent Written Requests
  - Azithromycin – ureaplasma pneumonia
  - Baclofen – spasticity
  - Lindane – safety
  - Lithium – mania in bipolar disorder
  - Lorazepam – sedation in ICU
  - Lorazepam – status
  - Sodium Nitroprusside – control of BP
  - Rifampin – methicillin resistant staph endocarditis

Current BPCA Success!

- RFC – RFP
  - Coordinating Center
  - Lorazepam – Status
  - Lorazepam – ICU Sedation
  - Nitroprusside – BP Control
- Proposals reviewed
  - Coordinating Center - Awarded
  - Lorazepam – Status - Negotiation
  - Lorazepam – ICU Sedation – Negotiation
  - Nitroprusside – to be reviewed at end of month

Current BPCA Success!

- BPCA colloquia 2003-2004
  - Clinical Trials in Pediatric Populations
  - Pediatric Pharmacoepidemiology – Measuring Frequency of Medication Use in Children
  - Dobutamine Usage in Neonates
  - Consent Issues in Pediatric Clinical Trials
  - Efficacy vs. Safety: Study Design Issues

Current BPCA Success!

- Special activities being conducted under BPCA -- Neonatal Clinical Trial Issues -- Workshop scheduled for March 29-30, 2004 in Baltimore to discuss trial issues
  - Pulmonary
  - Cardiovascular
  - CNS
  - Pain
  - Prioritization of therapeutic approaches

We need your input!

- Identify therapies needing studies in pediatric populations
  - Pediatric in-patient & out-patient conditions
  - Drugs & Biologics
- Designs to conduct the necessary pre-clinical and clinical studies
- Improve pediatric trials methodology
- Make data from the studies publicly available
- Label modification
- Practitioner education & Practice modification